can be found, for example, on page 5, lines 1-10; page 44, line 13, to page 46, line 29; page 94, lines 18-30; Table 3D, pages 106-115, and Figure 3A; Table 4D, pages 119-122, and Figure 3B; Table 5D, pages 127-137, and Figure 3C; Table 6D, pages 142-144, and Figure 3D; Table 7D, pages 149-156, and Figure 3E; Table 8D, pages 161-167, and Figure 3F; Table 9D, pages 172-175, and Figure 3G; Table 10D, pages 179-181, and Figure 3H. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth the amendment to the claims and specification in clean form above and in Appendix A, with marked up amendments indicated with brackets and underlining.

Applicants appreciate the Examiner's reconsideration of the species of NAD ligand and examination of NAD-related molecules.

Applicants bring to the Examiner's attention application serial No. 10/040,895.

Regarding the Title and Abstract

The Office Action indicates that the title and abstract are not descriptive. While Applicants believe that the original title and abstract are descriptive, the title and abstract have nevertheless been amended to conform with the Examiner's suggestion. Accordingly, it is respectfully requested that this objection be withdrawn.

Regarding the Drawings

Applicants appreciate Examiner Borin's time and indication in the telephone conference with Applicants' representative that the requirement for formal drawings was inadvertently inserted in the Office Action but was not required.

Regarding the Objection to the Claims

Claim 20 is objected to as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. This objection has been rendered moot by the cancelation of claim 20 and is respectfully requested to be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claim 20 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite is respectfully traversed. This rejection has been rendered moot by the cancellation of claim 20 is respectfully requested to be withdrawn.

Rejection Under 35 U.S.C. § 102

The rejection of claims 19-23 under 35 U.S.C. § 102(b) as allegedly anticipated by Carugo and Argos, Proteins: Structure, Function, Genetics 28:10-28 (1997), is respectfully traversed. Applicants respectfully submit that claims 19 and 21-23 are novel over Carugo and Argos.

Independent claim 19 is directed to a method for identifying polypeptide pharmacofamilies. The method includes the steps of determining bound conformations of a ligand bound to different polypeptides of a polypeptide family; and identifying two or more bound conformations of the ligand having substantially different bound conformations, thereby identifying at least a first bound conformation and a second bound conformation of the ligand. The method additionally includes the step of identifying other polypeptides of the polypeptide family exhibiting binding specificity for each of the first bound conformation and the second bound conformation of the ligand, thereby identifying at least two polypeptides having binding specificity for the first bound conformation and at least two polypeptides having binding specificity for the second bound conformation. The method further includes the step of determining conserved atoms of the polypeptides having binding specificity for the first bound conformation or the second bound conformation, wherein the conserved atoms are hydrogen bond donors or hydrogen bond acceptors to the bound ligand that are conserved between polypeptides that bind the first bound conformation or the second bound conformation but differ between a polypeptide that binds the first bound conformation and a polypeptide that binds the second bound conformation, thereby identifying at least two polypeptide pharmacofamilies exhibiting binding specificity for the two or more substantially different bound conformations of the ligand, wherein members of a pharmacofamily have conserved hydrogen bond donors and hydrogen bond acceptors to the bound ligand.

In contrast, the Carugo and Argos reference does not teach Applicants' claimed methods. In particular, the Carugo and Argos reference does not teach determining conserved atoms of the polypeptide that are hydrogen bond donors or acceptors that distinguish members of a pharmocofamily that binds a particular bound conformation of a ligand. Absent such a teaching, Carugo and Argos cannot anticipate the claimed methods. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 19-23 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement is respectfully traversed. Applicants submit that the specification provides sufficient description and guidance to enable the claimed methods.

The Office Action acknowledges that the specification provides enablement for a method using NADP but not for other nicotine amide-related molecules as ligands. The Office Action indicates that the prior art demonstrates that NADP binds to polypeptides in a variety of conformations but that the conformation of NAD is well conserved and does not change significantly upon binding to various polypeptides.

The Office Action refers to Bellamacina, FASEB J. 10:1257-1269 (1996), and indicates that this reference teaches that nicotinamide binding proteins all bind their NAD cofactor in the same location and orientation, with the cofactor itself adopting a similar extended conformation in every structure.

This assertion appears to refer to a statement made in the abstract of Bellamacina (penultimate sentence), "[T]he classical nicotinamide binding proteins all bind their cofactor in the same location and orientation, with the cofactor itself adopting a similar extended conformation in every structure." Bellamacina indicates that "nicotinamide binding proteins" are referred to as proteins that bind "NAD(P)+" (page 1257, second column, first paragraph, second sentence), which is indicated in footnote 2 as referring to both NAD^+ and $NADP^+$. Therefore, the description in Bellamacina of a similar extended conformation appears to refer both to NAD^+ and $NADP^+$, in contrast to the assertion in the Office Action that this description is referring to an NAD cofactor.

The Office Action also refers to Carugo and Argos, *supra*, as allegedly teaching that the protein-interactions are quite variable in NADP complexes and are largely conserved in complexes of NAD. The Office Action asserts that it is not predictable in regard to identifying pharmacofamilies based on variability in conformation of nicotine amide-related molecules other than NADP.

Applicants respectfully disagree with the assertion in the Office Action that the specification describes how to use NADPH as a ligand in identifying pharmacofamilies of polypeptides (Example I) but provides no working examples or guidance on how to practice the invention with nicotine amide-related molecules other than NADPH. The specification teaches in Example I the use of oxidoreductase structures that include the bound ligands NAD,

NADH, NADP and NADPH. Therefore, in contrast to the assertion in the Office Action, the specification does provide working examples using representative nicotinamide adenine dinucleotide-related molecules.

Moreover, the specification teaches that the use of the ligands NAD, NADH, NADP and NADPH allows the identification of pharmacophore families based on the conformation of the ligands (see Examples I and II). Eight pharmacofamilies were identified based on eight identified ligand conformations (Examples I and II and Figure 1). Accordingly, the specification does provide sufficient description and guidance to enable the claimed methods for nicotinamide adenine dinucleotide-related moleceles. Therefore, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The

Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

July 8, 2003
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APPENDIX A

In the specification:

On page 196, please delete the abstract on lines 2-18 and substitute therefor:

[The invention provides a method for identifying a pharmacocluster. The method includes the steps of (a) determining bound conformations of a ligand bound to different polypeptides, and (b) clustering two or more bound conformations of the ligand having substantially the same bound conformation, thereby identifying a pharmacocluster. The invention also provides a method for identifying a member of a pharmacocluster.] The invention **[also]** provides a method for identifying a polypeptide pharmacofamily. The method includes the steps of (a) determining bound conformations of a ligand bound to different polypeptides of a polypeptide family, and (b) identifying two or more bound conformations of the ligand having substantially different bound conformations, thereby identifying at least two polypeptide pharmacofamilies exhibiting binding specificity for the two or more substantially different bound conformations of the ligand.

In the claims:

19. A method for identifying polypeptide pharmacofamilies, comprising:

(a) determining bound conformations of a ligand bound to different polypeptides of a polypeptide family; **[and]**

(b) identifying two or more bound conformations of said ligand having substantially different bound conformations, **thereby identifying at least a first bound conformation and a second bound conformation of said ligand;**

(c) identifying other polypeptides of said polypeptide family exhibiting binding specificity for each of said first bound conformation and said second bound conformation of said ligand, thereby identifying at least two polypeptides having binding specificity for said first bound conformation and at least two polypeptides having binding specificity for said second bound conformation; and

(d) determining atoms of said polypeptides having a conserved location in three-dimensional space relative to said ligand and having binding specificity for said first bound conformation or said second bound conformation, wherein said conserved atoms are hydrogen bond donors or hydrogen bond acceptors to said bound ligand that are conserved between polypeptides that bind said first bound conformation or said second bound conformation but differ between a polypeptide that

binds said first bound conformation and a polypeptide that binds said second bound conformation, thereby identifying at least two polypeptide pharmacofamilies exhibiting binding specificity for said two or more substantially different bound conformations of said ligand**, wherein members of a pharmacofamily have conserved hydrogen bond donors and hydrogen bond acceptors to said bound ligand**.